THE RELATIONSHIP BETWEEN ESMOLOL AND THE ONSET AND DURATION OF ACTION OF SUCCINYLCHOLINE IN PATIENTS UNDERGOING GENERAL OR ORTHOPEDIC SURGERY

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Nurse Anesthesia at Virginia Commonwealth University

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List of Abbreviations

Ach.....acetylcholine

AchE.....acetylcholinesterase

AP.....action potential

ASA.....American Society of Anesthesiologists

dTc.....d-Tubocurarine

EMG.....electromyograph

Hz.....Hertz (cycles per second)

IBM-PC.....International Business Machines-Personal Computer

IV.....intravenous

kg.....kilograms

mcg.....micrograms

mcg/kg.....micrograms per kilogram

mcg/kg/min.....micrograms per kilogram per minute

min.....minute

mg.....milligrams

mg/kg.....milligrams per kilogram

msec.....millisecond

mV.....millivolts

s.....seconds

Sch.....succinylcholine

SEM.....standard error of the mean

TOF.....train-of-four

Abstract

THE RELATIONSHIP BETWEEN ESMOLOL AND THE ONSET AND DURATION OF ACTION OF SUCCINYLCHOLINE IN PATIENTS UNDERGOING GENERAL OR ORTHOPEDIC SURGERY

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The purpose of this study was to investigate a potential interaction between esmolol and succinylcholine. Specifically, the researcher investigated whether or not esmolol prolongs the onset and duration of action of succinylcholine (Sch). The investigator studied 25 adult, ASA I and II, male and female patients. Patients underwent orthopedic or general surgical procedures under general anesthesia requiring endotracheal intubation. All subjects received identical preoperative medication; glycopyrrolate 0.2 mg intravenous (IV).

Thirteen experimental subjects (Group I) received an infusion of esmolol 500 mcg/kg/min for 4 minutes prior to induction. The esmolol infusion continued at a rate of 300 mcg/kg/min for an additional 8 minutes before being discontinued. Twelve control subjects (Group II) received an infusion of 5% dextrose in water at an equivalent rate with respect to weight in kilograms (kg). Group II subjects received fentanyl 2-3 mcg/kg in place of esmolol to blunt the stress response during induction. All subjects received d-Tubocurarine (dTc) (0.05 mg/kg). Pre-oxygenation and induction with thiopental 3-5 mg/kg followed. Intubation was facilitated by IV administration of Sch 1.5 mg/kg. Anesthesia maintenance included a

nitrous oxide (66%) and oxygen (33%) mixture and intermittent boluses of 50-100 mg of thiopental to maintain unconsciousness.

The investigator placed five surface electrodes to monitor muscular response to ulnar nerve stimulation. The Puritan-Bennett NMT-221 electromyograph (EMG) generated a supramaximal train-of-four (TOF) stimulus to the ulnar nerve at a frequency of 2-Hz every 20 seconds. The investigator recorded the times in seconds (s) to 95% twitch suppression (onset) and to 50% and 90% recovery.

The time to 95% twitch suppression in Group I subjects was 78 s +/- 3 (mean +/- SEM). The time to 50% recovery was 697 s +/- 51 (mean +/- SEM) and the time to 90% recovery was 840 s +/- 51 (mean +/- SEM). The time to 95% twitch supression in Group II subjects was 67 s +/- 3 (mean +/- SEM). The time to 50% recovery was 614 s +/- 60 (mean +/- SEM) and the time to 90% recovery was 724 s +/- 65 (mean +/- SEM).

Statistical analysis revealed a significant slowing in onset of Sch induced muscle relaxation ($p<.045$). Conversely, there was no statistically significant delay in 50% ($p<.179$) and 90% recovery ($p<.109$). However, statistical analysis indicated that esmolol did prolong the recovery from Sch induced neuromuscular blockade. Further investigation of this potential interaction is warranted.

Chapter One

Introduction

Esmolol is a cardioselective, ultrashort-acting, beta-adrenergic antagonist (beta blocker) with a rapid onset. It is a safe and effective drug used to prevent or treat undesirable increases in heart rate and contractility (hypertension) that may occur during general anesthesia in response to increased sympathetic activity (Sung et al., 1986; S. Anderson, et al., 1986). Events during which these increases are most likely to occur include laryngoscopy and endotracheal intubation. Beta-blockade minimizes increases in heart rate and myocardial contractility, the primary determinants of myocardial oxygen consumption, by attenuating the positive chronotropic and inotropic effects of increased adrenergic activity (Menkhaus, et al., 1985; Liu, Gatt, Gugino, Mallampati, & Covino, 1986; Girard et al., 1985; Murthy, Patel, et al., 1986; W. Anderson, et al., 1986; Shulman, et al., 1985; Zsigmond, et al., 1985; Newsome, Roth, Hug, & Nagle, 1986; Ebert, et al., 1985).

Esmolol contains an ester linkage which leads to its rapid hydrolysis in the blood by esterases. Its rapid total body clearance also indicates that the blood esterase activity is the major factor responsible for its

rapid breakdown. The enzyme mediating the hydrolysis of esmolol appears to be an esterase that is distinct from plasma cholinesterase (Barabas, Zsigmond, & Kirkpatrick, 1986).

Succinylcholine (Sch) is a depolarizing muscle relaxant commonly used during general anesthesia. Succinylcholine has a rapid onset of profound but brief muscular relaxation. These characteristics make the drug useful during induction to facilitate endotracheal intubation. Succinylcholine is hydrolyzed by human plasma cholinesterase and the enzymatic hydrolysis is responsible for the termination of its toxicity. Barabas et al. (1986), in an *in vitro* study, found that esmolol and its metabolite inhibit plasma cholinesterase. Therefore, interference with this enzyme may effect the onset and duration of action of Sch.

In two studies examining the effect of esmolol on the duration of action of Sch *in vivo*, investigators reported conflicting results. McCammon, Hilgenberg, Sandage, and Stoelting (1985) found no effect on the onset or recovery time of Sch-induced neuromuscular blockade. Murthy et al. (1985) found that esmolol caused a small, but statistically significant, delay in recovery from the neuromuscular blockade of Sch. Murthy et al. (1985) described this phenomenon as having no clinical significance. This study investigated the relationship between these agents with respect to onset and recovery of neuromuscular blockade.

Statement of Purpose

The purpose of this study was to investigate whether the onset and duration of action of Sch is affected by esmolol.

Statement of the Problem

What is the effect of esmolol on the onset and duration of action of Sch in patients undergoing general or orthopedic surgery?

Hypotheses

1. Esmolol will not effect the onset of action of Sch in patients undergoing general or orthopedic surgery.

2. Esmolol will not effect the duration of action of Sch in patients undergoing general or orthopedic surgery.

Dependent Variable

The dependent variables were (a) onset to 95% neuromuscular blockade, (b) time to 50% recovery of neuromuscular blockade, and (c) time to 90% recovery of neuromuscular blockade.

Independent Variable

The independent variable was the esmolol infusion.

Definition of Terms

Beta-adrenergic blockade. Beta-blocking agents act by inhibiting the ability of endogenous catecholamines or sympathomimetic agents to interact effectively with beta-adrenergic receptor sites.

Duration of activity. The time interval in seconds, measured electromyographically, between Sch administration and 50% and 90% recovery of neuromuscular blockade.

Electromyogram. A non-invasive peripheral nerve monitor that quantitatively measures the muscular response following supramaximal nervous stimulation.

Electromyography. The monitoring and recording of muscular responses following nerve stimulation by supramaximal TOF stimuli repeated every 20 seconds. Square wave pulses of 0.1 msec duration are repeated at a rate of 2-Hz and quantified using the Puritan-Bennett 221 (Puritan-Bennett of Massachusetts, Inc., Wilmington, Massachusetts) neuromuscular transmission monitor.

Esmolol. An ultra-short-acting beta receptor antagonist that may be used during general anesthesia.

Nondepolarizing neuromuscular blockade. Nondepolarizing neuromuscular blocking agents compete with Ach for prejunctional and postjunctional receptor sites at the myoneural junction, thus inhibiting nerve transmission, resulting in muscle relaxation.

Onset of activity. The time interval in seconds, between the administration of Sch and 95% suppression of twitch response, measured electromyographically.

Potentiation. A more rapid onset of activity or increase in duration of Sch activity due to an interaction with esmolol.

Succinylcholine. A short-acting depolarizing neuromuscular blocking agent commonly used during general anesthesia.

Assumptions

1. Conduction along the stimulated motor nerve was not compromised.

2. The stimulated nerve innervated a muscle with an intact contractile mechanism.

3. A supramaximal stimulus was consistently delivered by the electromyograph.

4. The volume of distribution in each subject was normal.

5. Each subject possessed a normal acid-base status.

6. All patients had normal pseudocholinesterase and normal blood levels of pseudocholinesterase.

7. Subjects provided honest and accurate medical and drug histories.

8. The infusion pump consistently delivered the calculated dose of esmolol.

Limitations

1. An unknown or unrecognized underlying cause may be responsible for potentiation of neuromuscular blockade other than an interaction between esmolol and Sch.

2. The individual response to anesthetic drugs and neuromuscular blocking drugs is highly inconsistent.

3. Dibucaine and flouride numbers were not measured. Determinations of dibucaine permits diagnosis of the presence of atypical plasma cholinesterase. Patients with atypical plasma cholinesterase may have prolonged neuromuscular blockade (Kalow & Genest, 1957). Patients with a fluoride resistant enzyme or "silent enzyme" can have a markedly prolonged response to Sch (Whittaker, 1980). Cost constraints inhibited the performance of these tests.

Delimitations

1. Subjects could only be studied if they agreed to participate.

2. Premedication was limited to glycopyrrolate 0.2 mg IV.

3. Subjects required endotracheal intubation for the surgical procedure.

4. Body temperature of the patient was within one degree of normal on the Farenheit scale (98.6° F).

Conceptual Framework

Membranes and action potentials. Electrical potentials exist across the membranes of essentially all cells of the body. Some cells, such as nerve and muscle cells, are "excitable"--that is, capable of self-generation of electrical impulses to transmit signals along the membranes. When nerves are not transmitting nerve signals they are in a so-called "resting" state. In its resting state, the membrane is said to be "polarized" because of a large negative membrane potential that is present. The resting transmembrane potential of nerve cells and skeletal muscle fibers is approximately -90 millivolts (mV), that is, the inside of the cell is negative in relation to the outside of the cell. This electrical potential exists in response to the relative difference in the concentration of positively and negatively charged ions that exist intracellularly and extracellularly. This separation of charge is controlled and maintained by active and passive ion regulatory mechanisms (Guyton, 1986).

Rapid changes in electrical potential across nerve membranes is the basis for the action potential (AP). Depolarization is a rise in membrane potential toward a more positive value. The electrical potential difference becomes more positive until a critical value called the "threshold" (-65 mV) is reached. This sudden rise in membrane potential in a nerve fiber from -90 mV up to -65 mV results in the sudden

development of an AP. The AP generated excites adjacent portions of the membrane, resulting in propagation of the AP along the length of the nerve (Guyton, 1986). When the AP reaches the nerve neuromuscular junction (NMJ), a chemical message is transmitted to the muscle, and a mechanical contraction is triggered.

Neuromuscular junction. The Nobel Prize in medicine was awarded to Dale in 1936 for his proposal of the mechanisms of neuromuscular transmission. Dale was the first researcher to describe a chemically mediated synaptic transmission. Since then much has been learned about this structure in terms of its function and the effects of various diseases on its function. A knowledge of the anatomy and physiology of muscle, the contractile process, as well as the structure and physiology of the NMJ is necessary in order to understand the process of neuromuscular blockade. The following discussion is provided to acquaint the reader with some basic concepts of these processes.

Skeletal muscles are innervated by large, myelinated nerve fibers that come to an end at junctions called the NMJ. The NMJ is a specialized structure consisting of the motor nerve terminal, a motor endplate (an extension of the muscle fiber membrane), and the 20 to 30 nanometer space between them referred to as the synaptic cleft. Acetylcholine (Ach), a chemical neurotransmitter, normally functions here to transmit chemical messages from nerve cell terminal, across the synaptic cleft, to the muscle fiber (Guyton, 1986).

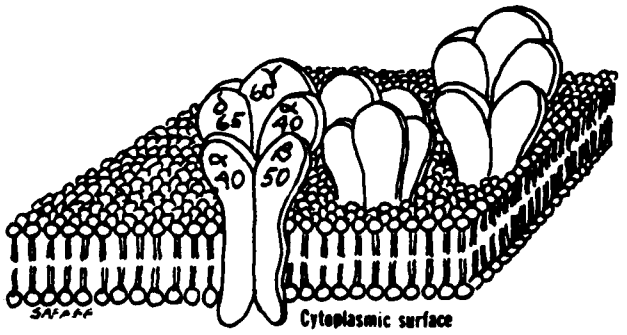
Acetylcholine in the NMJ. Vesicles exist in the nerve terminus in which Ach molecules are stored. Each vesicle contains approximately 10,000 molecules of Ach, an amount referred to as one quanta. In response to depolarization of the nerve terminal, vesicular exocytosis results in

the release of Ach into the synaptic cleft, a process referred to as quantal release. Vesicular exocytosis occurs in response to a voltage-dependent influx of calcium into the nerve terminal. The exact mechanism of calcium influx is unknown. However, the amount of Ach released in response to a nerve impulse can be altered by increasing or decreasing the extracellular calcium concentrations. After Ach is released, it diffuses across the synaptic cleft. Some Ach is hydrolyzed by existing acetylcholinesterase (AchE) in the cleft. The remainder reacts with receptor sites on the postjunctional membrane. Only one-half to two-thirds of the Ach released by a nerve impulse into the synaptic cleft reaches the receptor sites on the postsynaptic membrane. The receptor-Ach interaction results in a sudden increase in permeability to sodium, potassium, and other cations. Thus, the depolarization of the presynaptic terminal leads to a local depolarization of the postsynaptic membrane and the signal is said to be transferred to muscle fibers (Guyton, 1986).

Postjunctional membrane receptors. Specific receptors exist on the postsynaptic membrane within the NMJ. These receptors have been isolated and consists of five subunits which are designated alpha, beta, gamma, and delta as portrayed in Figure 1.

Each postsynaptic receptors is a protein. The receptor protein has a molecular weight of approximately 250,000 daltons (1 dalton = 1.657 X 10^{-24} Gm). There are two alpha subunits, weighing about 40,000 daltons apiece, and one each of the others, weighing about 50,000, 60,000, and 65,000 daltons, respectively (Standaert, 1986). This Ach receptor is termed an integral membrane protein because these five longitudinal subunits, when open, facilitates the movement of ions between the

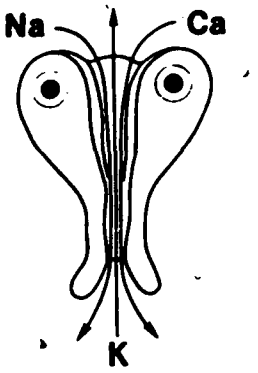
Figure 1. Acetylcholine receptor.



Note. From "Basic Physiology and Pharmacology of the Neuromuscular Junction" in R. D. Miller (ed.) Anesthesia (p. 843) by F. G. Standaert, 1986, New York: Churchill Livingstone.

intracellular and extracellular environments. As depicted in Figure 2, Ach (as indicated by two large, black dots) binds to both alpha subunits on the Ach receptor, and both alpha subunits must be occupied simultaneously for a conformational change to occur, thus forming the ion channel (Standaert, 1986). These postjunctional membrane receptors are ligand-activated rathar than voltage-activated gates, responding to Ach as the ligand. The surface-protruding portion of this channel protein acts as a receptor for Ach, and Ach in turn causes a conformational change in the channel. Channels open approximately 0.65 nanometers allowing sodium, potassium, and calcium to move through the channels. The sudden increase in ionic conductance results in depolarization of the endplate region, which in turn depolarizes adjacent regions of muscle cell membrane (Guyton, 1986).

Figure 2. The acetylcholine receptor in the open configuration.



Note. From "Donuts and Holes: Molecules and Muscle Relaxants" in R. L. Katz (Ed.), Muscle Relaxants: Basic and Clinical Aspects (p. 5) by F. G. Standaert, 1985, Orlando: Grune and Stratton.

Muscle contraction. The initiation of contraction of skeletal muscle begins with APs in the muscle fibers. These APs elicit electrical currents that spread to the interior of the fiber where they cause release of calcium ions from the sarcoplasmic reticulum. The calcium ions, in turn, initiate the chemical events of the contractile process (Guyton, 1986).

The basic unit of the skeletal muscular system is the muscle fiber, a multinucleated cell which is long and cylindrical in shape and contains bundles of filaments, termed myofibrils. Myofibrils are made up of two different protein molecules, or myofilaments, known as actin and myosin. These proteins are responsible for muscle contraction. Actin and myosin myofilaments overlap in such a way that their ends partially interdigitate. The thicker myosin filaments (large protein about 470,000

daltons) have small projections termed cross-bridges. It is the interactions between these cross-bridges with the actin filaments that produce muscle contraction. During contraction of the muscle fiber, the length of each set of myofilaments remains unchanged, but the degree to which the filaments interdigitate increases. The thin actin (small protein about 45,000 daltons) filaments are drawn into the thick myosin filaments resulting in muscle shortening (Murphy, 1983).

Calcium plays an important role in myofibril cross-bridging. When a muscle is stimulated, a rise in myoplasmic calcium concentration produces changes in the myofilament structure, allowing cross-bridge binding to the thin actin filament. After the cross-bridges bind to the actin, they undergo an energy dependent conformational change, thus moving the filaments in relation to one another. An energy yielding hydrolysis of adenosine triphosphate (ATP) provides the energy for the reaction (Murphy, 1983). It is the sum of millions of these conformational changes that result in the visible effect, muscle contraction. During surgery, muscle relaxants are given to suppress the sequence of events necessary for muscle contraction.

Muscle relaxants. There are two groups of neuromuscular blocking agents, non-depolarizing and depolarizing. Agents belonging to the non-depolarizing class include d-Tubocurarine (dTc), pancuronium, gallamine, vecuronium, and atracurium. An example of a depolarizing agent is Sch. The pharmacologic effect of each group is the interruption of the transmission of nerve impulses at the NMJ.

The mechanism of action of each group is distinctly different. Non-depolarizing muscle relaxants bind to the Ach receptor; however, they do not cause receptor activation. Instead, non-depolarizing muscle

relaxants inhibit neuromuscular transmission by two means. First, the muscle relaxant molecule may bind to the alpha subunit of the receptor protein, competing with and preventing Ach from binding to the Ach receptor (Standaert, 1986). Second, the molecule may, in a noncompetitive manner, obstruct the ionic channel by what is known as channel blockade, a physical impediment to ion flow (Colquhoun, 1986; Standaert, 1986). By either mechanism, depolarization cannot occur.

The depolarizing class of muscle relaxants bind to the Ach receptor. Relative to Ach, there is a higher concentration of Sch molecules available to interact with the receptor. The ion channel is held in the open position longer because of the relatively high concentration of drug in relation to Ach and slow clearance of these drugs by redistribution from the synaptic cleft. The depolarization of the endplate produced by Sch can be great enough to exceed the firing threshold of the muscle and to cause the muscle to contract. However, this situation does not persist because the muscle quickly accommodates the continued depolarization of the endplate and stops firing. The main surface of the muscle membrane regains its resting potential and the muscle returns to its resting state, even though the NMJ remains depolarized by the drug. Thus, depolarizing agents produce long-lasting depolarization of the NMJ and have a biphasic action on muscle; initially causing the muscle to contract and then allowing the muscle to relax. The apparent shift from excitation to relaxation of the muscle also is related to the duration of the drug's effect. The muscle remains relaxed because the membrane remains constantly depolarized (Standaert, 1986).

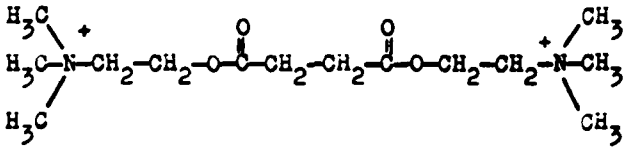
Neuromuscular blocking drugs may act at both the alpha subunits and the channels; however, a given drug may act preferentially at one site or

the other. For example, dTc, at low concentrations, is a relatively selective receptor blocker at the alpha subunits while high doses also act at channels (Stoelting, 1987). A small dose of dTc may be given approximately five minutes prior to the administration of Sch to prevent Sch induced fasciculations (Coppage, Wolfson, & Siker, 1972).

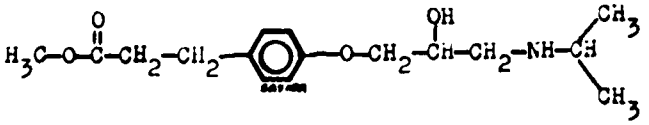
Succinylcholine. Sch is a depolarizing muscle relaxant. In 1906, Reid, Hunt, and de Taveau experimented with Sch, however, these researchers described only the cardiovascular effects of the compound. Since their experiments were on animals paralyzed with curare, they missed the neuromuscular blockade action of Sch. Experiments by Phillips (1949) first described its neuromuscular blockade properties. In 1952, Sch was introduced into the United States by Foldes.

Structurally, Sch is two molecules of Ach linked by an acetate and a methyl group (see Figure 3). The molecule is flexible, long, and slender so that it can bind to and activate cholinergic receptors, thus producing depolarization like Ach. Sch produces a rapid onset of profound but brief muscular relaxation in most patients, known as phase I blockade. Characteristics of phase I blockade are described in Table 1.

Figure 3. Chemical structure of succinylcholine and esmolol.



SUCCINYLCHOLINE



ESMOLOL

Table 1

Characteristics of phase I blockade

1. Onset is accompanied by fasciculations
2. Augmentation of NMB by anticholinesterases
3. Single twitch stimulus results in decreased contraction
4. Decreased amplitude but sustained response to continuous stimulation
5. Absence of posttetanic facilitation (the first twitches following a tetanus are larger than those twitches preceding it. The mechanism appears to reflect accumulation of calcium ions in the nerve terminal during tetanus.)

Note. From Succinylcholine, 1988, Di'Orio, S., unpublished manuscript, Virginia Commonwealth University, Richmond, Virginia.

Adverse side effects that may accompany administration of Sch include: (a) cardiac dysrhythmias, (b) hyperkalemia, (c) myalgia, (d) myoglobinuria, (e) increased intragastric pressure, (f) increased intraocular pressure, (g) increased intracranial pressure, and (h) sustained skeletal muscle contraction. These side effects may limit or even contraindicate the administration of Sch. As mentioned earlier, pretreating patients with nonparalyzing doses of non-depolarizing neuromuscular blockers such as dTc (defasciculating doses of dTc) may limit or abolish the occurrence of sustained skeletal muscle contraction and cardiac dysrhythmias, myalgia, as well as elevations of intragastric and intraoccular pressure (Stoelting, 1986). An outline of the disadvantages of Sch is provided in Table 2. Despite a long list of

Table 2

Disadvantages of Succinylcholine

Depolarization (endplate and muscle)
Fasciculation and increased abdominal pressure
Contracture
Denervated, extraocular, and jaw muscles
Potassium efflux and cardiac consequences (dysrhythmias)
Muscle pain (myalgia)
Changing nature of block
Tachyphalaxis and slow recovery
Other agonistic actions
Tachycardia and hypertension, other dysrhythmias
Sinus bradycardia and arrest
Idiosyncratic responses
Failure to metabolize succinylcholine
Atypical plasma cholinesterase
Exaggerated multisystem reactions
Malignant hyperthermia
Muscular dystrophies
Active metabolites
Drug interactions and complicating medical conditions
Cardiac dysrhythmias
Hyperkalemia in burn, renal failure, etc.
Other electrolyte imbalances
Cardiac glycosides
Contracture and cardiac dysrhythmias
Major neurologic lesions
Muscular dystrophies
Reduced metabolism of succinylcholine
Physiologic: pregnancy, obesity, age extremes
Cholinesterase inhibition
Increased metabolism of succinylcholine
Increased neuromuscular sensitivity:
myasthenia gravis, Mg
Reduced neuromuscular sensitivity:
myasthenia gravis

Note. From Succinylcholine: Its past, present, and future. In R. L. Katz (Ed.), Muscle Relaxants: Basic and clinical aspects (p. 74) by Lee, C., 1985, Orlando: Grune and Stratton.

disadvantages, certain desirable characteristics of the drug such as the short duration of action, rapid onset, low cost, and proven safety preclude the discontinuation of its use in anesthesia practice today.

Pharmacokinetics of Succinylcholine. In contrast to Ach which is rapidly hydrolyzed by AchE at the NMJ, Sch is not hydrolyzed by AchE. Succinylcholine is not eliminated from the NMJ until the drug is eliminated from the plasma. For this reason, the time it takes to clear the drug from the body, as a whole, is the principal determinant of how long the drug exerts its action. This clearance is very slow when compared to the destruction of Ach by AchE.

Since the drug molecules at the NMJ are not destroyed, they can react repeatedly with receptors, attaching to another as soon as they come off a first one. In this way, they repeatedly open channels and maintain a current flow across the membrane and a prolonged depolarization of the endplate (Standaert, 1986).

The extremely brief duration of action of Sch is primarily due to its rapid hydrolysis by plasma cholinesterase, an enzyme of the liver and the plasma (Miller & Savarese, 1986). According to Stoelting (1987), the initial metabolite, succinylmonocholine, is a much weaker neuromuscular blocker (1/20 to 1/80 as potent). In turn, it is metabolized to succinic acid and choline. Only a small fraction of the original intravenous dose actually reaches the NMJ because plasma cholinesterase has an enormous capacity to hydrolyze Sch at a very rapid rate. Neuromuscular blockade produced by Sch is terminated by its diffusion away from the NMJ into extracellular fluid because plasma cholinesterase is not present at the NMJ. Therefore, plasma cholinesterase influences the duration of action of Sch by controlling the amount of neuromuscular blocking drug that is

hydrolyzed before reaching the NMJ (Miller & Savarese, 1986; Stoelting, 1987).

Reductions in the hepatic production of plasma cholinesterase, drug-induced reductions in plasma cholinesterase activity, or the genetically determined presence of atypical plasma cholinesterase result in a slowed or absence of hydrolysis of Sch. As a result, Sch-induced neuromuscular blockade is prolonged (Viby-Mogensen, 1980). Liver disease must be severe before reductions in plasma cholinesterase production are sufficient to prolong Sch-induced neuromuscular blockade (Foldes et al., 1956). Potent anticholinesterase drugs are commonly used in insecticides, occasionally in the treatment of glaucoma and myasthenia gravis, and chemotherapeutic drugs such as nitrogen mustard and cyclophosphamide. Exposure to these agents may reduce plasma cholinesterase activity resulting in a prolonged neuromuscular blockade following administration of Sch. High estrogen levels, as observed in parturients at term, are associated with up to 40% decreases in plasma cholinesterase activity. However, the duration of action of Sch-induced skeletal muscle paralysis is not prolonged, presumably reflecting an increased volume of distribution of the drug at term (Leighton, 1986).

The presence of atypical plasma cholinesterase is often recognized only after an otherwise healthy patient experiences unusually prolonged neuromuscular blockade. Prolonged blockade following a conventional dose of Sch can last from one-half hour to several hours. Determinations of the dibucaine number, by qualitative serum analysis, permits diagnosis of the presence of atypical plasma cholinesterase (Kalow & Genest, 1957). There are many other genetically determined variants of plasma cholinesterase although the dibucaine-related variants are the most

important. It is paramount to recognize that the dibucaine number reflects the quality of plasma cholinesterase, that is, the ability to metabolize Sch, and not the quantity of enzyme circulating in the plasma.

Four isoenzymes of plasma cholinesterase have been electrophoretically separated. In addition, some individuals have a fifth isoenzyme and experience a shorter duration of action of Sch than those who lack this component (Sugimori, 1986). There are other abnormal plasma cholinesterases. For example, patients with a flouride-resistant enzyme, as described by Whittaker (1980), or "silent enzyme", can have a markedly prolonged response to Sch (Miller & Savarese, 1986; Oshita, Sari, Fujii, & Yonei, 1983). Sapsford and Bush (1986) describe a patient who developed prolonged apnea even though the plasma cholinesterase profile was demonstrated as being "normal genotype". Paradoxically, resistance to Sch due to increased activity of plasma cholinesterase has been reported but is relatively rare (Lee, 1985).

Drug Interactions. Various drugs can interfere with the action of muscle relaxants. These drugs may exert their action proximal to the NMJ, at the NMJ, distal to the NMJ, or a combination of the sites (Viby-Mogensen, 1985). An interaction at the NMJ itself may principally take place at three sites a) the nerve terminal, b) the postsynaptic membrane, or c) in the synaptic cleft. Many drugs act at one or more than one of these sites.

Succinylcholine demonstrates a variety of effects on agents commonly used in the practice of anesthesia. For example, Donati and Bevan (1983) concluded that with Sch infusions of ninety minutes or less, isoflurane accelerates the onset of tachyphylaxis and phase II neuromuscular blockade without affecting Sch requirements. Similar results were reported

previously with enflurane and halothane. Stoelting (1986) explained that ester local anesthetics compete with other drugs for plasma cholinesterase thus introducing the possibility of a prolonged drug effect from Sch. Finally, Murthy et al. (1985) described the prolongation of Sch induced neuromuscular blockade in patients who were receiving esmolol during general anesthesia. Any drug with anticholinesterase activity will have an effect in the synaptic cleft and interfere with the enzymatic hydrolysis of Ach (Viby-Mogensen, 1985).

Cimetidine effect on Sch duration of action is a controversial subject. Kambam, Dymond, and Krestow (1987) demonstrated that administration of cimetidine, an H_2-receptor antagonist, significantly prolonged the duration of action of Sch. In one of the patients given cimetidine, the time for initial recovery of twitch after Sch administration was 45 min. Twitch height returned to 50% of control 57 min after the administration of Sch. The plasma cholinesterase level and fluoride number in this patient were in the normal range. However, Woodworth et al. (1989), found that cimetidine, at therapeutic blood levels, had no significant effect on the duration of Sch-induced neuromuscular blockade. Woodworth also demonstrated that preoperative administration of cimetidine did not effect plasma cholinesterase activity.

Succinylcholine is hydrolyzed by human plasma cholinesterase and the enzymatic hydrolysis is responsible for the termination of its toxicity. Barabas et al. (1986), in an <u>in vitro</u> study, found that esmolol and its metabolite inhibit plasma cholinesterase. Therefore, esmolol may increase the toxicity of Sch.

Electrolytes. Clinical reports and experimental studies have clearly shown that, in patients with certain diseases or conditions, an exaggerated release of potassium in response to Sch may occur, occasionally of such magnitude that cardiac arrest ensues. Conditions especially susceptible to hyperkalemic response from Sch are burns, trauma, nerve damage, neuromuscular disease, closed head injury, intraabdominal infections, and renal failure (Miller & Savarese, 1986).

Acid-base balance. Acid-base balance has been shown to be an important consideration in the augmentation of neuromuscular blockade with Sch. A decreased pH (called acidosis), shortens the duration, while an elevated pH (called alkalosis), prolongs the duration (Ham, 1979). The pH can be varied considerably during induction of anesthesia by hyperventilation. This hyperventilation can lead to alkalosis, therefore, prolonging the effect of Sch (Coppage et al., 1972).

Temperature. A decreased body temperature prolongs the duration of action of Sch: an elevated body temperature shortens the duration of action of Sch (Moore, 1982).

Weight. The duration of action of Sch appears to be determined primarily by the level of plasma cholinesterase activity in the blood and the volume of the extracellular fluid space. Compared to non-obese patients, obese patients have both increased plasma cholinesterase levels and an increased extracellular fluid space. These factors should increase the Sch requirement of obese patients (Bentley, Borel, Vaughan, & Gandolfi, 1982).

Physiology of the autonomic nervous system. An understanding of the anatomy and physiology of the autonomic nervous system is important to comprehending the action of pharmacological agents. A complete

description of this system is beyond the scope of this paper. The reader is encouraged to reference such textbooks as Guyton (1986), Berne and Levy (1983), Merin (1986) or Schreiber (1987) for a review of the autonomic nervous system. Only basic concepts concerning this research are provided below.

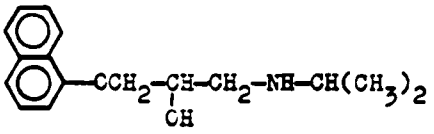
Beta-adrenergic receptor antagonists (beta blockers). The introduction of beta blocking agents was one of the most important therapeutic advances in recent medical history. These agents exhibit a broad and growing spectrum of clinical therapeutic application for disorders such as angina pectoris, hypertension, dysrhythmias, chronic glaucoma, and migraine. Developed by Black and coworkers in the 1960's, propranolol was the first beta blocker introduced clinically (Dimich & Eisenkraft, 1987).

Catecholamines interact with the adrenoreceptors of "target" cells by activating the enzyme adenylcyclase, which is located on the plasma membrane. Activated adenylcyclase increases the formation of cyclic AMP, which in turn produces the multiple physiologic and metabolic responses. Beta blocking agents act by inhibiting endogenous catecholamines or sympathomimetic agents from interacting effectively with receptors (Dimich & Eisenkraft, 1987).

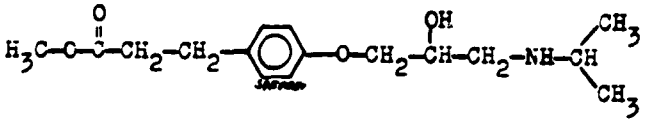
The beta blocking agents may be divided into two broad categories including those selective or specific for alpha receptors and those effective at beta receptors. Competition between the beta blocking agents and catecholamines for the adrenoreceptor is a function of the structural similarity between beta agonist and antagonist. For example, propranolol has a similar chemical configuration to the pure beta adrenergic agonist, isoproterenol. The structures of the antagonists propranolol and esmolol

are given in Figure 4. Beta blockade is competitive and can be reversed by increasing the dose of beta agonist (Dimich & Eisenkraft, 1987).

Figure 4. Chemical structures of propranolol and esmolol.



Propranolol



Esmolol

Beta receptors are subdivided into two groups. $Beta_1$ receptors are found in the heart, kidney, and adipose tissue. Blockade of $beta_1$ receptors reduces resting exercise-induced increases in heart rate, decreases the rate of spontaneous depolarization of ectopic pacemakers, and prolongs atrioventricular conduction time. Therefore, cardiac output is decreased, mechanical systole is prolonged, and blood pressure is decreased; while ventricular volume and end-diastolic pressure may rise (Dimich & Eisenkraft, 1987).

$Beta_2$ receptors are found primarily in vascular and bronchial smooth muscle, in the gastrointestinal system, and in skeletal muscle. Blockade of $beta_2$ receptors results in bronchoconstriction, peripheral vasoconstriction (including coronary arteries), and inhibition of glycogenolysis. Beta blockade has also been shown to alter the affinity of hemoglobin for oxygen, shifting the dissociation curve to the right

which results in increased oxygen delivery to the tissues (Dimich & Eisenkraft, 1987).

Cardioselectivity. The majority of the beta blocking drugs used clinically, including propranolol, share the property of blocking both $beta_1$ and $beta_2$ receptors. However, some are termed "cardioselective", since these drugs interact primarily with $beta_1$ receptors. An example of a $beta_1$ selective agent is esmolol. Cardioselectivity is relative and can be lost when higher doses of these drugs are administered (Dimich & Eisenkraft, 1987).

Contraindications. Patients with acute disease treated with intravenous administration of drugs benefit most when the agent has a quick onset and short half-life. These features allow rapid attainment and easy titration of therapeutic effects and also rapid recovery of effects should adverse effects occur or when treatment is no longer indicated (Abrams et al., 1985). Beta blockers possess a number of adverse effects which may preclude their use in certain clinical situations. The adverse effects include hypotension, severe bradycardia, myocardial depression, and brochoconstriction. The more common conditions which may be exacerbated by beta blockade are (a) acute bronchial asthma, (b) chronic obstructive lung disease, (c) sick sinus syndrome, (d) A-V block--second and third degree heart block, (e) severe congestive heart failure, (f) vascular insufficiency, and (g) advanced renal or liver disease (Dimich & Eisenkraft, 1987). Currently available beta-blockers have elimination half-lives between 2 and 6 hours. These adverse effects, therefore, may dissipate slowly. Ultra-short acting beta blockade, such as with esmolol, could provide safe acute beta blockade in patients who are at risk for treatment with the longer acting beta blockers (Abram et

al., 1985). Studies in human volunteers confirmed that esmolol functions as an ultra-short acting beta blocker with a half-life of 9.2 minutes (Sum et al., 1983).

Esmolol. Esmolol is a useful drug for preventing or treating increased blood pressure and heart rate that occur intraoperatively. Responses to noxious stimulation, as during intubation of the trachea, are effectively attenuated by esmolol (Menkhaus et al., 1985). Administered as a continuous intravenous infusion, 200-500 mcg/kg/min, beginning 5 minutes before induction of anesthesia, esmolol prevents increases in heart rate associated with noxious stimulation in patients undergoing coronary artery bypass graft operations (Girard et al., 1985). In these anesthetized patients, esmolol does not change mean arterial pressure, atrial filling pressures, or cardiac output. There is minimal alteration in peripheral vascular resistance because $beta_2$ receptor function remains intact during administration of esmolol. This contrasts with non-selective beta blockers, such as propranolol, that not only attenuate circulatory responses, but may also increase peripheral vascular resistance (Stoelting, 1987).

Pharmacokinetics of esmolol. The short duration of esmolol is due to rapid hydrolysis by esterases in the red blood cell cytosol (Sum et al., 1983). Five minutes after discontinuing the drug, heart rate is unchanged from predrug values. The elimination half-life of esmolol is 9.2 minutes in healthy subjects receiving a continuous infusion of 400 mcg/kg/min over two hours (Sum et al., 1983). Plasma concentrations of esmolol are usually not detectable 15 minutes after discontinuing the drug. (Anderson, Blanski, et al., 1986). Plasma esterases responsible for hydrolysis are distinct from plasma cholinesterase. Metabolites of esmolol hydrolysis

are an acid called ASL-8123, which posseses 1/1,500th the beta blocking activity of esmolol and methanol (Reynolds, Gorczynski, & Quon, 1986). Blood levels of methanol following an infusion of esmolol at a rate of 150 mcg/kg/min for 24 hours approximate endogenous levels and were less than 2% of toxic levels (Blanski, Lutz, & Laddu, 1988).

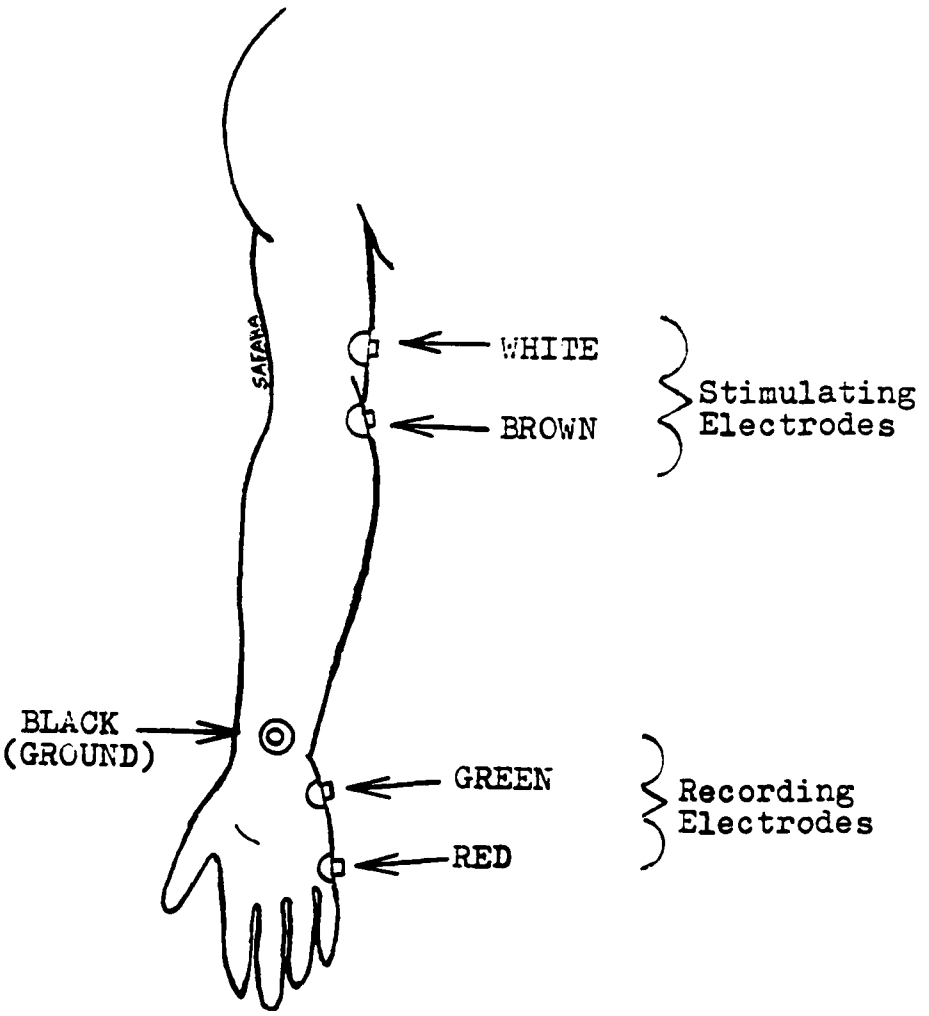
Adverse effects of esmolol. The benefits of the administration of esmolol during general anesthesia far outweight the risks. Adverse effects associated with administration of esmolol are, in general, mild and reversible. For example, hypotension could be rapidly eliminated by discontinuing the infusion. This makes esmolol a desireable drug for use in modulating the potentially detrimental changes in adrenergic tone during the perioperative period, especially in patients with coronary artery disease or in those with an unstable cardiovascular status (Murthy, Hwang, et al., 1986). Irritation at the site of infusion has been reported in eight percent of patients studied by Blanski et al. (1988). Blanski et al. (1988) also demonstrated that skin irritation is avoided when concentrations less than 10 mg/ml are used.

Monitoring neuromuscular blockade. The only practical, noninvasive method of studying neuromuscular transmission is stimulation of a peripheral motor nerve with simultaneous observation and measurement of the corresponding muscle response (Ali & Savarese, 1976). The purpose of monitoring is to quantify neuromuscular blockade. An individual patient response to any drug is highly variable, hence, peripheral neuromuscular monitoring makes it possible to adjust drug dosing to individualize the patient's needs for relaxation. To monitor neuromuscular function, electrodes are most often placed along a superficial peripheral nerve, and attached to a peripheral nerve stimulator. Ideally, to ensure stimulation

of all muscle fibers innervated by the stimulated nerve, a supramaximal stimulus must be applied (Lee & Katz, 1980). This supramaximal stimulus is found by gradually increasing the pulse of energy applied to the nerve until a maximal response is obtained. This maximal stimulus is then increased by 15 to 20 percent, and is termed the supramaximal stimulus. Assuming that electrical conduction along the motor nerve is intact, propagation of supramaximal stimulus must result in contraction of all muscle fibers supplied by the motor nerve (Ali & Savarese, 1976). This method of monitoring neuromuscular function is not practical in everyday clinical use because it is expensive and requires a large amount of equipment, but is more exact and more appropriate for use in clinical research.

Supramaximal stimulation of the ulnar nerve at the elbow and the recording of the muscular response via surface electrodes applied over the the abductor pollices muscle (hypothenar EMG) will evoke EMG measurements (see Figure 5). Five electrodes are placed; two recording electrodes, two stimulating electrodes, and one ground electrode. The recording electrodes are placed with the active, or negative electrode, over the motor point of the abductor pollices, and the indifferent electrode placed over its tendon. The ground electrode is placed between the stimulating and recording electrodes. Ground electrodes are useful in reducing the 60-Hz interference emitted by electrical devices. The stimulating electrodes are place at the elbow, within the ulnar groove. Movement artifact is reduced by securing the patient's hand with an immobilization strap.

Figure 5. Lead placement for electromyography.



Summary. The sequence of events necessary for muscle contraction to occur is extremely complicated. Propagation of an AP along a motor nerve results in the release of the neurotransmitter Ach from the nerve terminal. Ach in turn activates ion channels on the postsynaptic membrane, causing depolarization of the postsynaptic membrane and establishing the conditions necessary for muscle contraction to occur. Succinylcholine attaches to each of the alpha subunits of nicotinic cholinergic receptors and mimics the action of Ach by depolarizing postjunctional membranes.

Esmolol, a beta-adrenergic antagonist, is used during general anesthesia to blunt the stress response associated with induction. It is an ultra-short acting agent since the molecular configuration contains an ester function on the aromatic ring that allows for rapid metabolism of esmolol at the site of esterification (Anderson, Blanski, et al., 1986).

When used concomitantly during general anesthesia, a potential drug interaction exists. Esmolol may prolong the duration of action of Sch. A possible explanation of this potentiation lies in the pharmacokinetics of both agents. Succinylcholine is hydrolyzed by plasma cholinesterase while esmolol is hydrolyzed by different esterases. However, esmolol may interfere with plasma cholinesterases and hence interfere with the hydrolysis of Sch, thus prolonging its action.

Chapter Two

Review of Literature

The possibility of a drug interaction during simultaneous administration of esmolol and Sch was studied by two groups of investigators (McCammon et al., 1985; Murthy et al., 1985). In both studies, the inhibition of neuromuscular transmission by Sch and subsequent recovery was evaluated in patients infused with esmolol and those infused with a placebo. The infusion rates for both studies were identical. Esmolol was infused at a rate of 500 mcg/kg/min for 4 minutes prior to induction with thiopental and then decreased to 300 mcg/kg/min and infused for an additional 8 minutes. However, the two studies include many differences in research methodologies.

McCammon et al. (1985) studied sixteen ASA I or II patients scheduled for non-cardiac surgery under general anesthesia. All patients were premedicated 60 to 90 minutes prior to induction with 0.15 mg/kg of morphine and 0.4 mg of scopolamine intramuscularly and 300 mg of cimetidine orally. The eight patients in the experimental group received esmolol as described above. Eight control patients received an infusion of five percent dextrose in water at a rate of 1 ml/kg/min for 12 minutes. McCammon's protocol included metocurine 30 mcg/kg IV to control fasciculations, induction with thiopental 4 mg/kg IV, and administration

of Sch 2 mg/kg following loss of lid reflex. Maintenance of anesthesia was provided with enflurane (1 to 1.5% inspired) and a nitrous oxide (60%) and oxygen (40%) mixture following intubation. McCammon's group stimulated the ulnar nerve with a Grass S-48 stimulator through 25 gauge needle electrodes inserted at the wrist. Four single supramaximal stimuli in a TOF of 0.15 millisecond duration were administered at a frequency of 2-Hz every 15 seconds. The EMG response was monitored through an active electrode over the abductor pollices muscle. Muscular twitch responses were continuously recorded to determine the time to 95% twitch depression and to 50% and 90 recovery. McCammon found no difference between the two groups in the time to 95% twitch depression or to 50% and 90% recovery. The time to 95% twitch depression in the experimental group was report to be identical to the control group value of 64 s +/- 5 (mean +/- SD). The time to 50% and 90% recovery in the experimental group was 786 s +/- 54 (mean +/- SD) and 1,038 s +/- 72 (mean +/- SD), respectively. The time to control group recovery for 50% and 90% was 702 s +/- 48 (mean +/- SD) and 1,026 s +/- 84 (mean +/- SD), respectively. These researchers concluded that in patients with normal plasma cholinesterase activity and phenotypic make-up (serum dibucaine and fluoride numbers were measured preoperatively), esmolol does not affect the onset and recovery time of Sch-induced neuromuscular blockade.

Murthy et al. (1985) studied the effects of esmolol on circulatory response to intubation and Sch-induced neuromuscular blockade in human subjects undergoing general anesthesia. Sixteen patients were studied. Eight patients in the control group received an infusion of five percent dextrose in water for 12 minutes. The control infusion rate was identical to the esmolol infusion rate based on the subjects' weight. Eight

experimental subjects received an esmolol infusion as described above. Premedication included 0.1 mg/kg of morphine and 0.2 mg of glycopyrrolate intramuscularly 1 hour prior to induction for all subjects. Murthy's protocol included no agent to control fasciculations, thiopental 4 mg/kg IV for induction, and Sch 1 mg/kg IV. Subjects were maintained with a nitrous oxide (60%) and oxygen (40%) mixture following intubation. Each subject's left forearm and hand were immobilized in a splint. Surface electrodes were used to stimulate the ulnar nerve with supramaximal stimuli of 0.2 milliseconds duration at 5 second intervals. Adduction of the thumb was recorded using a force transducer. Times to 20, 40, 60, and 80% recovery of twitch response were measured. The time to 80% recovery was 553 s +/- 56 (mean +/- SD) in the esmolol group and 374 s +/- 26 (mean +/- SD) in the control group. Murthy et al. (1985) concluded that esmolol caused a small but statistically significant delay in the recovery of twitch response. In the same study, these individuals measured the hemodynamic response during induction. It was concluded that esmolol attenuates intubation-induced tachycardia and offers cardioprotective effects for patients with coronary artery disease.

Explanations for these conflicting results are not clear. A possible explanation may be the differences in their measuring instruments and the muscles measured. According to Donati and Bevan (1984), EMG and twitch tension may be used interchangeably to evaluate neuromuscular blockade. However, each method represents different physiological events that are not always quantitatively identical. The force transducer measures mechanical events. The EMG measures electrical events. These two instruments also differ since each device may be recording events from different muscles or different parts of the same muscle. Additionally,

different muscles have different sensitivities to neuromuscular blocking drugs and this may also be true of various parts of the same muscle. Furthermore, according to Ali and Savarese (1976), the evoked mechanical twitch response is less sensitive to Sch induced blockade than the electrical EMG. Therefore, evoked twitch tension monitoring may reveal complete neuromuscular recovery upon return to baseline levels. To the contrary, the information obtained from the EMG may still indicate substantial muscle weakness. The discrepancies between EMG and twitch tension are unlikely to influence patient management, but in the research setting, the differences are large enough to be important. Dose response relationships obtained with EMG will be different from those obtained with muscular twitch. Upon examination of the data above, differences in dose response relationships in these studies is immediately evident. Comparing McCammon's (1985) findings of 786 s at 50% recovery to Murthy's (1985) findings of 553 s at 80% recovery makes this point even clearer. Murthy's methodology demonstrated a shorter time period to a greater degree of recovery, consistent with what one would expect to find, since Murthy measured evoked twitch tension.

The exact mechanism of potentiation of Sch by esmolol as proposed by Murthy (1985) is not well understood and deserves further investigation. Several possible mechanisms have been suggested. First, Barabas, Kirkpatrick, and Zsigmond (1984) suggest esmolol is metabolized by an esterase present in the erythrocytes, while Sch is inactivated by pseudocholine esterase present in the plasma. Thus, some overlap of affinity of plasma cholinesterase for these two substrates is possible. In 1986, this finding was shown to be true by Barabas et al. Second, Murthy, Patel, et al. (1986) suggests redistribution from the

extravascular space to the vascular space may play a significant role in the removal of Sch from the motor end plate. Therefore, decreased cardiac output, attributable to esmolol-induced beta blockade, may slow the rate of redistribution and hence delay the rate of recovery from neuromuscular blockade. Third, an interaction between propranolol and Sch was studied by Wislicki and Rosenblum (1967). Propranolol was found to intensify the neuromuscular blocking effects of Sch. Esmolol may share these effects with propranolol (Murthy, Patel, et al., 1986).

Chapter Three

Methodology

Research Design

The research design was a true experimental design. Two groups were compared to determine if esmolol affected the onset and recovery of Sch-induced neuromuscular blockade. Subjects were randomly selected from the daily operating room schedule and assigned to study groups on an alternating basis.

Population, sample, and setting

The probability sample came from a population of adult inpatients, without regard for age, gender or race, at a metropolitan university based hospital. ASA I or II subjects scheduled for either orthopedic or general surgery, requiring endotracheal intubation and lasting greater than one hour, were studied during the time span beginning January, 1989 and ending March, 1989. The researcher performed the study in one of twenty-five average sized, modern operating rooms, all of which were equally suitable.

Exclusion criteria

Exclusion criteria for sample selection include items found in Table 3. Other exclusion criteria include a) nil per os (NPO or nothing by mouth) less than 8 hours, b) emergency procedures, c) procedures expected to last less than 1 hour, and d) situations where use of thiopental was contraindicated.

Investigational Procedure

Research began after the study was approved by the university's Committee on the Conduct of Human Research (CCHR). Complete confidentiality was maintained during the study. Informed consent was obtained from all subjects (see Appendix A). The sequence of the study was as follows (also see Table 4 for an brief outline of the study protocol):

1. An intravenous catheter, a minimum size 18-gauge, was inserted in the upper extremity for infusion of a 5% dextrose in lactated Ringer's solution, as well as for infusion of esmolol or control solutions.

2. The patient's hand, wrist, and elbow were prepped with benzoin for placement of stimulating and recording electrodes in accordance with the manufacturer's recommendations (see Figure 5).

3. All patients received glycopyrrolate 0.2 mg intravenously approximately 30 minutes prior to induction.

4. Upon arrival in the operating room the patients were identified and carefully assisted onto the operating table. Basic physiologic monitors were then applied and included an electrocardiogram, an automatic blood pressure measuring device, a pulse oximeter, and a precordial stethoscope. Baseline hemodynamic readings were recorded while the EMG

Table 3

Exclusion criteria

Pregnancy
Morbid obesity, defined by Blass (1981) as anyone weighing twice the predicted weight for age, sex, body build, and height according to the Metropolitan Life Insurance tables.
History of atrial flutter or fibrillation
A-V conduction block greater than first degree
Myocardial infarction within six-months prior to surgery
Systolic blood pressure less than 100 mm Hg
Diastolic blood pressure less than 50 mm Hg
History of congestive heart failure
History of atypical plasma cholinesterase or prolonged neuromuscular blockade under general anesthesia
Chronic obstructive pulmonary disease, bronchial asthma, or history of bronchospasm
Clinical or laboratory evidence of severe renal, hepatic, or neurological disease
History of drug allergy to beta-andrenergic blocking agents
Concurrent drug therapy with beta-blockers other than propranolol, beta-adrenergic stimulants, alpha-andrenergic blockers, alpha-adrenergic stimulants, antiarrythmics, digoxin, digitoxin, adrenergic augmenting psychotropic drugs, reserpine, and guanethidine.

Note. From "Cardiovascular effects of esmolol in anesthetized humans" by P.G. Menkhaus et al., 1985, Anesthesia and Analgesia, 64, p. 328.

Table 4

Study protocol

Time (min)	Events
Zero	Esmolol 500 mcg/kg/min IV initiated
	Patient being preoxygenated
	dTc 0.05 mg/kg IV administered
Four	Decrease esmolol to 300 mcg/kg/min IV
	Oxygenation continues
Five	fentanyl 2-3 mcg/kg IV administered (Group II only)
	Thiopental 3-5 mg/kg IV administered
	Lid reflex absent
	Obtain baseline EMG readings
Six	Airway assured
	Sch 1.5 mg/kg IV administered
	EMG readings initiated
Seven	Endotracheal intubation
	After correct tube placement assured nitrous oxide 66%
	with oxygen 33% administered
Seven and on	Thiopental 50-100 mg IV bolus administered as necessary
Twelve	Discontinue esmolol infusion
	Continue EMG measurements until 90% recovery
Study complete	Add inhalation agent, other agents as necessary

electrodes were attached. Patients were oxygenated with 100% oxygen via a face mask and a semi-closed circuit anesthesia system.

5. At time zero, experimental subjects began receiving a loading dose of esmolol, 500 mcg/kg/min. An infusion of 5% dextrose in water, at an equivalent rate with respect to volume based on body weight, was administered to group II subjects (see Table 5).

Table 5

Study groups

Group	Class	Infusion
I	Experimental	esmolol 500 mcg/kg/min for 4 min then esmolol 300 mcg/kg/min for 8 min
II	Control	Equivalent volume of 5% Dextrose in Water (placebo) for 12 min

6. Just after the esmolol infusion was started (time zero), all subjects received dTc 0.05 mg/kg IV to prevent fasciculations which may interfere with the accuracy and quality of the EMG function.

7. At 4 minutes the esmolol infusion rate was decreased to 300 mcg/kg/min. Group II subjects were administered fentanyl 2-3 mcg/kg.

8. At 5 minutes thiopental 3-5 mg/kg was administered IV to induce anesthesia and to protect against discomfort during baseline EMG measurement.

9. Once the lid reflex was absent, the EMG was activated until a stable baseline of supramaximal stimuli was obtained.

10. Once an airway was assured, Sch 1.5 mg/kg was administered.

11. Endotracheal intubation was performed 1 minute after the Sch was given. Intubation was accomplished in 30 seconds or less.

12. All patients received a mixture of nitrous oxide (66%) and oxygen (33%) and 50 to 100 mg bolus of thiopental as necessary to maintain unconsciousness until 90% recovery was obtained. At that time an inhalation agent was added as necessary.

Instrumentation

The Puritan-Bennett 221 neuromuscular transmission monitor (NMT) was used in this investigation. The NMT-221 was designed for measuring neuromuscular blockade by electrically stimulating a peripheral nerve and displaying the resulting integrated electromyograph. The NMT-221 features an automatic search capability for the maximal stimulus current level needed to activate all the fibers of the stimulated muscle. Once found, this maximal current is then the supramaximal stimulus current. After determining the supramaximal stimulus, the NMT-221 stimulates the patient with a train-of-four (TOF) to set the 100% reference level. While operating, the NMT-221 delivers a TOF stimulus every 20 seconds and compares the resulting response with the initial reference values. The NMT-221 displays a T1 ratio, that is the measured first twitch displayed as a percentage of the reference. The NMT-221 is connected in parallel to an IBM-PC that receives the neuromuscular transmission input, integrates it, and displays the data on a graph where the abscissa represents time and the ordinate represents the per cent of control. The graphic data is interpreted and the time to loss of 95% function is automatically calculated (Russell & Hummel, 1988).

Data Analysis

The experimentor recorded the age, gender, weight, ASA category, procedure, total thiopental dose, and the time to onset and recovery of Sch for each subject (see Appendix B). The compiled information provided the following data (a) the number of seconds until to 95% suppression of the twitch response following the intubation dose of Sch, (b) the number of seconds until 50% recovery of neuromuscular blockade following the intubating dose, and (c) the number of seconds until 90% recovery of neuromuscular blockade following the intubation dose. A statistical procedure called the two-tailed t test was used to examine the difference between the groups with respect to age and weight.

The experimentor calculated the mean and standard error of the mean for the times to onset and recovery for each group. The researcher also performed a test of significance to determine if the differences in responses were due to a specific factor. Since some of the factors are continuous variables (age, weight) analysis of covariance was utilized rather than just analysis of variance. Three separate responses were measured (time, in seconds, to 95% blockade, 50% recovery, and 90% recovery), therfore, three separate, but similar analyses, were performed. The results of the analysis were also utilized to test the null hypotheses (H_o). The level of significance was $p<.05$. Reject the H_o if $p<.05$ (not due to chance).

Chapter Four

Results

Subjects

A total of 27 patients participated in this study. There were 13 subjects in Group I and 12 subjects in Group II. Two subjects were eliminated from the study. One subject was underdosed with esmolol and the other subject developed a prolonged neuromuscular block of 44 minutes. The author postulated the subject with prolonged neuromuscular blockade had an unidentified plasma cholinesterase deficiency or an atypical plasma cholinesterase enzyme. Serum analysis of dibucaine was recommended.

There were six males and six females in the control group. The experimental group included five males and eight females. Table 6 outlines the physical characteristics of subjects including the mean, standard error of the mean, and range for age and weight of subjects in each group. A two-tailed t test reveals no significant difference ($p<.44$) with respect to weight. However, a significant difference for age was calculated ($p<.02$). This significant factor was corrected for utilizing analysis of covariance as the statistical investigational tool.

Table 6

Physical Characteristics of Subjects

Group	Mean Age (years)	Range (years)	Mean Weight (kg)	Range (kg)
I[a]	30.5 +/- 2.4	18 - 43	75.4 +/- 3.7	55 - 100
II[b]	40.7 +/- 3.4*	27 - 66	70.8 +/- 4.5	55 - 105

Mean +/- S.E.M. [a]n = 13. [b]n = 12. *Significantly different from group I, $p<.02$

Analysis

Table 7 is a descriptive chart that outlines the times to onset of neuromuscular blockade and 50% and 90% recovery of neuromuscular blockade for group, gender, ASA category, age, and weight of all subjects. The researcher grouped and analyzed the data in this manner to investigate the possibility of these factors effecting the variables measured.

Table 7

Descriptive Statistics

	N	Onset (s)	Time 50% (s)	Time 90% (s)
Group I	13	77.7 +/- 2.7	697.5 +/- 51.1	840.4 +/- 51.1
Group II	12	67.1 +/- 3.0	613.7 +/- 59.6	723.7 +/- 64.9
Male	11	67.4 +/- 3.0	780.9 +/- 60.2	909.1 +/- 56.4
Female	14	76.6 +/- 2.8	560.1 +/- 34.8	686.4 +/- 46.5
ASA I	9	76.1 +/- 2.8	687.2 +/- 62.7	809.4 +/- 73.4
ASA II	16	70.6 +/- 3.1	640.4 +/- 51.0	770.3 +/- 52.1
Ages 18 - 34	13	72.9 +/- 2.9	681.2 +/- 60.0	807.1 +/- 66.4
Ages 35 - 66	12	72.3 +/- 3.5	681.2 +/- 52.5	763.5 +/- 54.0
Weight 55 - 70	12	72.5 +/- 3.4	602.7 +/- 46.3	725.8 +/- 56.2
Weight 75 - 105	13	72.7 +/- 2.9	716.4 +/- 61.8	847.9 +/- 59.3

Mean +/- S.E.M. s = seconds. Age in years. Weight in kg.

The investigator utilized an analysis of covariance to determine if the difference in responses was due to one of the factors described in Table 7. The author analyzed these factors with respect to the three intervals measured. Analysis of covariance was utilized for two reasons. First, analysis of covariance, rather than simply an analysis of variance, was the appropriate statistical tool since two of the factors (age and weight) are continuous measures. Second, age was a significant factor between study groups. Analysis of covariance corrects for this factor and determines if age is a significant variable with respect to onset and recovery of Sch-induced neuromuscular blockade.

Onset

The researcher investigated the possibility of an interaction between group, gender, ASA, weight, and age and the time to onset. Table 8 describes the calculated analysis of covariance.

Table 8

Analysis of Covariance With Respect to Onset

Factor	p
group	.045 *
gender	.041 *
ASA	.389
age	.689
weight	.267

*$p < .05$

Time to 50% Recovery

The experimenter repeated the above analysis for time to 50% recovery. Table 9 summarizes the analysis of covariance.

Table 9

Analysis of Covariance With

Respect to 50% Recovery

Factor	p
group	.179
gender	.003 *
ASA	.250
age	.897
weight	.873

*p<.05

Time to 90% Recovery

The author also performed analysis of covariance with respect to time until 90% recovery (see Table 10).

Table 10

Analysis of Covariance With

Respect to 90% Recovery

Factor	p
group	.109
gender	.005 *
ASA	.333
age	.900
weight	.996

*p<.05

Significance of Gender

Table 11 summarizes the statistical significance of gender. Initially, gender is separated with respect to groups. The overall results of the study are then listed. Finally, gender is separated from the groups to illustrate the overall effect of this variable.

Table 11

Statistical Significance of Gender

Group	N	Gender	Onset (s)	Time 50% (s)	Time 90% (s)
I	5	Male	72.8 +/- 4.7	838.0 +/- 84.4	970.0 +/- 62.9
I	8	Female	80.8 +/- 2.9	609.6 +/- 43.0	759.4 +/- 58.5
II	6	Male	63.0 +/- 3.2	733.3 +/- 86.9	858.3 +/- 88.9
II	6	Female	71.2 +/- 4.7	494.2 +/- 48.5	609.6 +/- 58.4
I	13		77.7 +/- 2.7	697.5 +/- 51.1	840.4 +/- 51.1
II	12		67.1 +/- 3.0	613.7 +/- 59.6	723.7 +/- 64.9
	11	Male	67.5 +/- 3.0	780.9 +/- 60.2	909.1 +/- 56.4
	14	Female	76.6 +/- 2.8	560.1 +/- 34.8	686.4 +/- 46.5

Mean +/- S.E.M. s = seconds. Summary of p values for gender are--Onset ($p<.041$), Time 50% ($p<.003$), Time 90% ($p<.005$).

Chapter Five

Discussion

The purpose of this study was to investigate whether the onset and duration of action of Sch is affected by esmolol. The researcher proposed two hypotheses (a) esmolol will not effect the onset of action of Sch in patients undergoing general or orthopedic surgery and (b) esmolol will not effect the duration of action of Sch in patients undergoing general or orthopedic surgery. Based on the statistical analysis of the data collected the author must reject (a) and fail to reject (b).

Table 11 clearly illustrates the effect of gender on the onset and recovery of Sch induced neuromuscular blockade in both control and experimental groups. Using the statistical results the author concluded (a) esmolol significantly slows the onset of Sch induced neuromuscular blockade regardless of gender, (b) males are significantly faster to onset of Sch-induced neuromuscular blockade then are females, (c) the time to 50% recovery of Sch-induced neuromuscular blockade is significantly faster for females than males, and (d) the time to 90% recovery of Sch-induced neuromuscular blockade is also significantly faster for females than males. Additionally, there was evidence ($p<.179$ for 50% recovery and $p<.109$ for 90% recovery), although not statistically significant, indicating esmolol prolonged the duration of action of Sch in both

males and females.

The results of this study differed from previous studies. McCammon et al. (1985) did not find a significant difference between the esmolol and control group with respect to onset. Both McCammon et al. (1985) and Murthy et al. (1985) did not analyze their data with respect to gender. Therefore, the results of this study cannot be compared to previous researchers with respect to this variable.

In attempting to explain the findings of this study, plasma cholinesterase, the enzyme responsible for Sch metabolism, was considered first. Low plasma cholinesterase activity would make patients more susceptible, and high cholinesterase activity more resistant to the pharmacological and toxic effects of Sch. That is, Sch would exert its effect faster and sustain its effect longer if the plasma cholinesterase activity was diminished. The time to onset of Sch induced neuromuscular blockade was faster and the time to recovery of Sch-induced neuromuscular blockade was longer in male subjects. Thus, the author concluded that the activity of plasma cholinesterase was diminished in males.

The author performed a review of the literature to investigate this explanation. Evidence to the contrary was discovered. Shannor, Van Hees, Baart, Erdos, and Foldes (1961) studied the influence of sex on human plasma cholinesterase <u>in vitro</u>. These investigators observed a statistically significant difference between the plasma cholinesterase activity of young, healthy males and females. These researchers reported the activity of female plasma cholinesterase with Sch to be 64 to 74% of the male activity. This would indicate males are less sensitive to the toxic effects of Sch than females. Therefore, the time for onset in males

should be longer and the time to recovery should be shorter in males. This is opposite to the findings obtained by this study.

McCammon et al. (1985) and Murthy et al. (1985) failed to report a factor analysis on their study groups. In fact, these two researchers did not describe their study groups beyond their numerical size and ASA category. Therefore, this researcher cannot compare this factor analysis to their studies.

Weaknesses identified in both the McCammon et al. (1985) and Murthy et al. (1985) studies are the sample size and the control of variables. The McCammon group, as well as the Murthy group, both had experimental groups consisting of eight subjects. The number of subjects in the controls groups was also eight. This researcher's experimental group consisted of thirteen subjects and the control group contained twelve subjects. Although the groups studied are larger than previous investigations, the total number of subjects is still not optimal. Therefore, inferences concerning the entire population cannot be drawn since the size of the study group did not exceed 30 subjects.

Both investigating groups introduced variables into their methodology that may have an effect on the onset and duration of action of Sch induced neuromuscular blockade. McCammon et al. (1985) premedicated subjects with cimetidine. Administration of cimetidine, an H_2-receptor antagonist, is associated with a direct inhibition of liver microsomal enzymes and a decrease in liver blood flow resulting in a variety of clinically significant drug interactions. One such interaction is with Sch. Kambam et al. (1987) demonstrated a potentiation of Sch recovery in patients administered cimetidine preoperatively. These researchers found the duration of action of Sch two to two and one-half times longer in

patients given cimetidine. Cook, Stiller, Chakravorti, and Mannenhira (1988) performing an in vitro study, found that at clinically relevant concentrations, cimetidine does not inhibit hydrolysis of Sch by plasma cholinesterase. Cook et al. (1988) postulated that the mechanisms of potentiation of Sch by cimetidine may occur at the NMJ. However, the exact mechanism for the potentiation of Sch action caused by cimetidine still needed to be investigated. In 1989, Woodworth et al. examined this reported interaction. Woodworth et al. (1989) found no significant effect of cimetidine on the duration of action of Sch or the plasma cholinesterase enzyme. Clearly, this subject remains controversial.

McCammon et al. (1985) administered enflurane, a volatile anesthetic agent, to subjects following induction of anesthesia. Enflurane may accelerate the onset of phase II neuromuscular blockade caused by Sch (Donati & Bevan, 1983). Since enflurane and Sch are reported to interact in an adverse manner, the introduction of yet another uncontrolled variable may effect the results of their study.

Both Murthy et al. (1985) and McCammon et al. (1985) premedicated their patients with morphine. In 1985, Lowenthal et al. reported that Morphine, when concomitantly administered IV with esmolol, increases the steady-state blood levels of esmolol by 46%.

This researcher was extremely careful to control as many variables as possible. Premedication was limited to glycopyrrolate for all subjects. The research protocol was followed carefully. One major difference between study groups was the administration of fentanyl 2-3 mcg/kg, in place of esmolol, to control subjects. However, Moore (1982) showed that fentanyl does not prolong the duration of action of Sch.

During three experimental group trials anesthetists assisting in this research felt it necessary to introduce isoflurane into the breathing circuit. The initiation of isoflurane occurred after 50% recovery of Sch-induced neuromuscular blockade was measured in each of these incidents. The researcher does not believe this had any adverse effect on the results of the study. The time necessary to achieve adequate concentrations of isoflurane in muscle tissue, resulting in increased muscle relaxation, was not nearly proximated (Donati & Bevan, 1983).

Conclusion

Previous researchers who have noted a prolongation of neuromuscular blockade by Sch suggested that concomitant administration of esmolol may interfere with the plasma cholinesterase enzyme. One cannot rule out this possibility completely. Plasma cholinesterase may be inhibited to some degree, however marked variations seem unlikely. This mechanism is not likely to be the cause of the prolongation of Sch-induced neuromuscular block when used in combination with esmolol (Murthy, Hwang, et al., 1986). The results of this investigator's study provided additional evidence to support this conclusion. First, if esmolol did interfere with plasma cholinesterase, more Sch would be available to exert its effect. In terms of onset, more Sch would accumulate faster since less is being broken down. This would result in a faster onset of neuromuscular blockade. However, a statistically significant slowing of onset was demonstrated in this study. A possible explanation of this paradoxical finding may be a problem in the methodology. The researcher simultaneously marked the time of injection of Sch by depressing a key on the computer keyboard as Sch was injected by another anesthetist. A delay in the drug reaching the

circulation may have occurred depending on the speed of injection, the distance the drug traveled in the IV tubing, the speed of the IV infusion, the height of the IV bag, and the coordination of the event. Second, previous research indicates that males have higher quality enzyme than females. Therefore, males should break down Sch faster and the time to recovery should be shorter. This was not the case in this study. Females consistently recovered faster than males. This evidence supports this authors contention that plasma cholinesterase interference is not the major cause of Sch potentiation when used concomitantly with esmolol.

It is known that the redistribution of Sch from the extravascular space to the vascular compartment plays a significant role in the removal of Sch from the NMJ. A decrease in cardiac output and blood flow to skeletal muscles, as is induced by esmolol, may slow the redistribution of Sch. Thus, the time to recovery from neuromuscular blockade will be prolonged. The author can only conclude that the negative chronotropic effect of the beta-blocker, esmolol, slows the redistribution of Sch from the NMJ, thereby prolonging the duration of action of Sch. The reason for a greater prolongation in males rather than females cannot be explained.

Summary

In summary, is was found that esmolol delayed the onset of Sch induced neuromuscular blockade. Female subjects experienced a slower onset and faster recovery. There was no statistically significant delay in Sch-induced neuromuscular blockade during concomitant administration of esmolol. However, there was ample clinical evidence to suggest such an interaction and further investigation of this possibility is warranted.

Suggestion for Further Research

The methodology should be refined to eliminate the error that may have occurred due to the inconsistent delivery of Sch into the circulation at a specific moment. Prospective researchers may consider giving either both groups fentanyl in equivalent doses or no fentanyl to either group. Future investigators could perform the research protocol on groups containing either all males or all females. This would eliminate gender as a possible variable. This researcher also suggests recording the change in heart rate from baseline after initiating esmolol infusion. Comparing heart rate to speed of recovery could test the hypothesis: The more esmolol attenuates the heart rate, the longer Sch-induced neuromuscular block is prolonged. A positive correlation would support the slow rate of distribution hypothesis.

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Appendix A

Appendix A

CONSENT

THE RELATIONSHIP BETWEEN ESMOLOL AND THE ONSET AND DURATION OF ACTION OF SUCCINYLCHOLINE IN PATIENTS UNDERGOING GENERAL OR ORTHOPEDIC SURGERY

Introduction

The purpose of this study is to determine the effects of esmolol on succinylcholine when administered intravenously during general anesthesia (while going to sleep). Specifically, the onset (start of drug action) and duration of action (time to recovery) of succinylcholine will be measured and recorded to see if esmolol effects succinylcholine. The person responsible for the project is Paul J. Safara, a Senior Nurse Anesthesia Resident at the Medical College of Virginia. His phone number is (804) 786-9808. Mr. James Embrey, C.R.N.A., and Dr. Judith Fabian, Department of Anesthesiology, M.C.V., are supervising this study. The Department of Anesthesiology phone number is (804) 786-1324.

Both esmolol and succinylcholine are short acting drugs and are routinely used in anesthesia. Esmolol is used to treat cardiac dysrhythmias as well as to control increases in heart rate and blood pressure associated with the induction of anesthesia (going off to sleep), endotracheal intubation (insertion of breathing tube in the windpipe after going off to sleep), and surgical manipulation. Succinylcholine is used to relax muscles during intubation. In this study, you will receive

either esmolol and succinylcholine or sugar water and succinylcholine. The drug dosage will be calculated based on your weight. The medication will be introduced into your vein through an intravenous catheter (an intravenous catheter is required for all patients undergoing general anesthesia). Observations of the drug's interaction will be made while you go off to sleep.

Benefits

The benefits of participation in this study are to me and to medical science. The induction of general anesthesia can be stressful to your body (increasing heart rate and blood pressure). Esmolol is a drug which has been proven to reduce stress related increases in heart rate and blood pressure while going off to sleep. In past studies, investigators have found giving esmolol prolongs the effect of succinylcholine. Other investigators disagreed with this finding. In this study, you will be given one of the combination of medications described above. You will go off to sleep in the same fashion as others not participating in this study. Your participation will benefit medical science because it will help determine the effects of esmolol on succinylcholine during the induction of general anesthesia. Understanding these principles will enable clinicians to administer anesthesia more safely and effectively.

Alternative Therapy

If you do not participate in this study, the only difference may be that you do not receive esmolol. A medication, such as a narcotic, may be used intravenously to decrease the stress of going off to sleep. Muscle relaxation with succinylcholine intravenously may also be used. Various other muscle relaxants are also available and may be used.

As described above, you may receive the sugar water and succinylcholine combination. In this situation the stress of going off to sleep will be controlled with other medications. Your anesthesia provider will know what combination of medicine you are receiving. Sugar water may be thought of as a placebo. The risk of receiving a placebo may mean that your condition might not change or may worsen.

Risks, Inconveniences, Discomforts

Your participation in this study does not expose you to additional risks beyond those associated with the use of esmolol. Esmolol's safety is well proven and it is commonly used in anesthesia. The major side effect stems from the beta-blockade properties of the medication which may cause hypotension (low blood pressure). Other side effects include sweating, nausea and vomiting, dizziness, somnolence, and allergic reactions. Prolonged neuromuscular blockade has been reported.

An electronic twitch monitor will be attached to electrodes on your arm. You may feel small electric impulses running down your arm and into your fingers causing muscles in part of your hand to contract. These impulses will be of such a small quantity that little or no discomfort is anticipated.

Cost of Participation

There are no extra costs for your participation in this study. You will be responsible for all routine anesthesia and operating room costs.

Research Related Injury

You understand that in the event of any physical and/or mental injury resulting from your participation in this research project, Virginia Commonwealth University will not offer compensation.

Confidentiality of Records

Your name and identity will be kept confidential. You give permission for the results of this study to be used for teaching or for publication in scientific literature, with confidentiality being maintained.

Withdrawal

You have been given an opportunity to ask questions concerning this research project, and all questions have been answered to your satisfaction. You understand that you may, at any time, revoke your consent, and withdraw from this study without further question.

The nature, purpose, method, risks, benefits, and alternatives have been thoroughly explained to you. After being given this information, you do hereby give consent to participate in the research project entitled: THE RELATIONSHIP BETWEEN ESMOLOL AND THE ONSET AND DURATION OF ACTION OF SUCCINYLCHOLINE IN PATIENTS UNDERGOING GENERAL OR ORTHOPEDIC SURGERY

SIGNATURE_____ DATE_____

WITNESS_____ DATE_____

Appendix B

Appendix B

THE RELATIONSHIP BETWEEN ESMOLOL AND THE ONSET AND DURATION OF ACTION OF SUCCINYLCHOLINE IN PATIENTS UNDERGOING GENERAL OR ORTHOPEDIC SURGERY

Data Collection Sheet

Patient ID Number_____ Date_____ ASA I II III

Procedure_____ Age____ Wt_____kg

Male/ Female

Pentothal Dose _____mg total

Esmolol group/ Control Group

EMG Data:

_____ seconds to 95% block

_____ seconds to 50% recovery

_____ seconds to 90% recovery

Comments: _____

_____

_____

_____

_____

Appendix C

Appendix C

Raw Data

Group	Trial	Weight (kg)	ASA	Gender	Age (yrs)	Onset (s)	Time50% (s)	Time90% (s)
Control								
	1	55	I	Female	66	68	620	705
	2	70	II	Male	38	60	680	795
	3	60	II	Female	38	50	310	390
	4	75	II	Male	32	55	1,080	1,200
	5	55	I	Female	45	82	470	515
	6	55	II	Male	55	58	720	855
	7	90	I	Male	34	77	520	610
	8	70	I	Female	54	72	615	780
	9	105	II	Male	36	66	540	680
	10	75	II	Male	27	62	850	1,010
	11	60	II	Female	34	80	525	630
	12	80	II	Female	30	75	425	515
Experimental								
	1	Underdosed		Trial	Not	Used		
	2	80	II	Male	39	64	970	1,010
	3	80	II	Male	38	88	750	955
	4	65	I	Male	22	62	945	1,080
	5	100	I	Male	37	77	980	1,070
	6	55	II	Female	32	85	495	605
	7	75	I	Female	19	74	640	735
	8	75	II	Male	23	73	545	735
	9	60	II	Female	22	72	575	680
	10	65	I	Female	43	83	550	685
	11	90	II	Female	39	92	567	875
	12	70	I	Female	18	90	845	1,105
	13	70	II	Female	35	80	485	610
	14	95	II	Female	29	70	720	780
	15	Prolonged		Trial	Not	Used		

Vita

Paul J. Safara [redacted], and is an American citizen. He graduated from Martin Van Buren High School, Queens Village, New York, in 1976. He received his Bachelor of Science in Nursing from Adelphi University, Garden City, New York, in 1983. In August, 1987, while a Captain on active duty in the United States Air Force, he was sponsored by the Air Force Institute of Technology to attend the Department of Nurse Anesthesia, School of Allied Health Professions, Virginia Commonwealth University.